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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/353,126	07/14/99	MALINOW R	CSHL.005.01U

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EXAMINER	
TURNER, S	

ART UNIT	PAPER NUMBER
1647	6

DATE MAILED: 05/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/353,126	Mallnow et al.
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication app ars on the cover sheet with the corresp ndenc addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 2-16-01

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1 and 3-13 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1 and 3-13 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. The amendment filed 2-16-01 has been entered into the record and has been fully considered.

2. Claim 2 is canceled. Claims 1 and 3-13 are pending.

3. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Rejections Maintained

Claim Rejections - 35 USC § 112 first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-13 stand rejected under 35 U.S.C. 112, first paragraph, as set forth in Paper No. 3 mailed 10-12-00 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the claim amendments obviate the rejection, that the methods use "mutant hippocampal cells having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells" and thus avoids the rejection with respect to various mutations and unpredictable or unreliable effects because the cells are required to demonstrate the defined and desired effects as claimed in the method. Applicants further argue, that Parent et al., teaches

that transgenic mice expressing FAD-linked A246E human PS1 variants showed significant increase of fEPSP slope amplitude following tetanic stimulation, that Parent et al., teach that mutant hippocampal cells have predictably and reliably enhanced synaptic potentiation upon tetanic stimulation as compared to wild-type hippocampal cells, p. 61, column 1, lines 12-14 and that undue experimentation is not required. Applicants concede that there is no difference between mutant and wild-type cells following non-LTP inducing stimuli as disclosed in Figure 1, p. 3, line 30 through p. 4, line 9, but that differences do exist between mutant and wild-type cells following LTP inducing tetanic stimulation, Figures 2 through 5. Applicants argue with respect to MPEP 2107.02 I that all that is required is a reasonable correlation between eletrophysiology and a screening method for candidate drugs, that the metes and bounds of treatment are irrelevant and that the scope of the claims is a screening method and not a treatment. Applicants further submit that the reasons the screening method is related to identifying drugs is that the measurement of a reduction of aberrant signaling may be used to indicate the presence of a candidate drug as disclosed at p. 3, lines 22-26. Applicants argue that the invention is not directed to in vivo protocols that it is well known in the art that screening methods are discovery methods, that there are numerous murine models of Alzheimer's Disease, namely Lamb et al., 1999, Janus et al., undisclosed publication year and Bournemann et al., 200, that human or in vivo trials are not required, that any method that reduces the pool of candidate drugs before clinical trials has merit as a method of screening drugs, and that therapeutic indexes and treatments are not required.

Applicants arguments filed 2-16-01 have been fully considered but are not persuasive. With respect to applicants argument that the cells are required to have enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells and thus do not possess unreliable or unpredictable effects, the examiner notes that applicants exemplification of such cells is limited to a single mutation effect. As previously noted the art of predicting protein function based upon variant structure is unpredictable, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. Further with respect to applicants claims, the specification fails to teach a scope of presenilin mutations which exhibit enhanced synaptic potentiation upon tetanic stimulation in comparison to wild-type cells. Thus the scope of the claims is not commensurate with the scope of enablement. With respect to Parent et al., it is noted that applicants point to support for enablement of applicants claims as Parent teaches (as supported in the Parent et al., abstract) that following "theta burst stimulation or high frequency stimulation, input-specific LTP in Mtg (mutant transgene) animals had a larger initial amplitude and was more persistent than in WtTg or NTg (wild-type or nontransgenic) animals. However, it is also noted in the Parent et al., abstract, Figure 1 and Table 1 that basal synaptic transmission was unaltered in Mtg, WtTg or Ntg mice including maximum fiber volley amplitude, fEPSP amplitude, slope, and paired-pulse facilitation (a form of repeated/tetanic stimulus). Thus, the effects do not appear to be correlated with enhanced synaptic potential following general tetanic (repeated) stimuli since paired pulse facilitation was no different among groups. Instead it appears that the fEPSP differences observed in mutant presenilin cells occurs only following stimuli which induce long

term potentiation, which elements are not specifically claimed. Applicants are further directed to the teachings of Kandel et al., Principles of Neural Science, Elsevier, 3rd Ed., 1991, pp. 206-209, and 1019-23, in particular to the requirements and description of long term potentiation. With respect to applicants arguments concerning the enablement of the screening method to identify candidate drugs for the treatment of Alzheimer's Disease, the examiner understands applicants suggestion to be that the administration of drugs identified as capable of reducing synaptic potentiation (LTP) in mutant hippocampal cells is probable and desirable to treat Alzheimer's. However, in contrast to this suggestion the art recognizes that Alzheimer's patients exhibit deficiencies in learning and memory. Thus it appears that a drug which reduces synaptic potentiation, (a model of learning and memory) would be counterintuitive to treating Alzheimer's Disease. Instead it would appear that such drug would likely lead to an exacerbation of the learning and memory deficits associated with the disease. There is no evidence that the enhanced fEPSP slope in the presenilin mutant cells contributes to Alzheimer's or is aberrant as applicant's suggest. Further there is no recognition that blockade of synaptic potentiation is beneficial for screening drugs for the treatment of Alzheimer's Disease. An alternative suggestion could be that the observation is a mere epiphenomena or a compensating response resulting from the predisposing effects of the presenilin mutation. The in vivo model's referred to by applicants have not been evaluated as to content as the references have not been provided to the examiner. However, the appendix summaries do not appear to support the correlation of reduced synaptic potentiation with improved learning and memory as desired in Alzheimer's patients and

treatments. It is also noted that the references appear to be post-filing date evidence which is insufficient to provide a nexus for enablement at the time of the invention.

Claim Rejections - 35 USC § 112 second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6 and 8-9 stand rejected under 35 U.S.C. 112, second paragraph, as set forth in Paper No. 3 mailed 10-12-00 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "significant change" in said claims is a relative term which renders the claims indefinite. The specification does not provide a standard for ascertaining the requisite degree of change required to exactly constitute "significant change", and one skilled in the art would not be reasonably apprised of the scope of the invention.

Applicants argue that MPEP 2107.01 VII does not support the requirement of statistical significance to support utility.

Applicants arguments filed 2-16-01 have been fully considered but are not persuasive. The examiner notes that the rejection of record is one of indefiniteness and not of utility as referred to in MPEP 2107.01. The relevant question is what are the relevant metes and bounds of the claims as they recite a "significant change." The skilled artisan is not able to discern applicants intent as to whether the recited change is required to be statistically significant, at what

level or in contrast merely different in any particular characteristic. The terminology "significant change" is indefinite without reference or guidance as to what a significant change is.

Rejections Necessitated by Amendment

Information Disclosure Statement

4. The information disclosure statement filed 2-16-01 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1 and 3-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 09/193,221.

Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims specific to hippocampal cells and PS-1Δ9 mutation are anticipated by the corresponding claims generically drawn to a presenilin gene mutation. The claims remain largely identical with respect to the recited method steps although instant claims have now been amended such that they do not overlap ipsis verbis.

7. Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite "with a candidate drug that is not an antibody," which recitation constitutes new matter. The specification does not support the specific exclusion as claimed. Antibodies may be drugs and used as such. Applicants should point to the specification where support may be found for the exclusion of antibodies as drugs.

8. Claims 1 and 3-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite "contacting mutant hippocampal cells, with a presenilin gene mutation". It is unclear to the artisan how the cell is contacted with a gene mutation. It appears applicant may be intending to recite a cell having a presenilin gene mutation. Applicants should particularly note the elements of the claims which are intended to be contacted.

9. Claims 1 and 3-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. The claims recite a "presenilin gene mutation", however no "gene" is described.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). However, the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed," (*See Vas-Cath* at page 1116) because as set forth in Lewin, Ed., Genes IV, Oxford Univ. Press, 1990, p. 810, a gene is the segment of DNA involved in producing a polypeptide chain and includes regions preceding and following the coding region as well as intervening sequences. In contrast, applicants specification merely discloses cells having the PS-1 Δ9 mutation (recognized by the artisan as disclosed for example in Crook et al., Nature Medicine 1998 April 4(4):452-5). Thus, the encompassed sequences of the PS-1 Δ9 mutation appear to be described, however that encompassed by a presenilin gene is not, for example including upstream and downstream sequences of the "gene" which direct expression in the organism. Thus, the specification does not disclose the "gene" as claimed or enable the artisan recognition of the encompassed mutations. With the exception of the PS-1Δ9 mutation, the skilled artisan cannot envision the

detailed structure of the encompassed components and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Status of Claims

7. No claim is allowed.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
April 26, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud